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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/570,556	09/29/2006	Samuel J. Danishefsky	2003080-0210 (SK-1156-US)	9739

24280 7590 04/01/2009

CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
04/01/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No.	Applicant(s)	
	10/570,556	DANISHEFSKY ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15 and 17-39* is/are pending in the application.

4a) Of the above claim(s) *5,6,24,26,28-34 and 36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-15,17-23,25,27 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

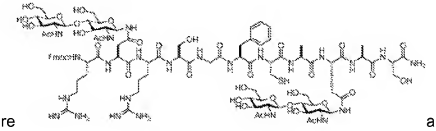
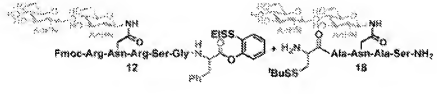
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to non-final rejection filed on December 17, 2008 is acknowledged. Claims 2, 16 and 40 have been cancelled. Claims 1, 3-15 and 17-39 are pending in this application. Applicant elected with traverse of Group I and elected polyfunctionalized peptide structure  and species 

for peptide acyl donor and peptide amino acceptor, and for an immunogenic carrier, applicant elects Keyhole Limpet Hemocyanin (KLH) in the reply filed on June 2, 2008. The traverse was not found persuasive, and the restriction requirement was deemed proper and made FINAL in the previous office action. Claims 5-6, 24, 26, 28-34 and 36-39 remain withdrawn from further consideration as being drawn to nonelected species and invention, pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. The polyfunctionalized peptide of claim 35 appears to be free of prior art. Search was extended to the broad Markush of claim 1, and prior art was found. **Claims 1, 3-4, 7-15, 17-23, 25, 27 and 35 are examined on the merits in this office action.**

This application contains claims 5-6, 24, 26, 28-34 and 36-39 drawn to an invention nonelected with traverse in the reply filed on June 2, 2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn Rejection

1. Rejection of claim 1 under 35 U.S.C. 112, 2nd as being indefinite for reciting, "...under suitable conditions to effect ligation" is hereby withdrawn in view of Applicant's amendment to the claim.

2. Rejection of claim 1 under 35 U.S.C. 112, 2nd as being indefinite for reciting, "...wherein two or more non-adjacent amino acids are independently substituted with a moiety having the structure: with the proviso that the peptide sequence between any two consecutive, non-adjacent, amino acids bearing A-L^1-moiety comprises at least one cysteine residue", is hereby withdrawn in view of Applicant's amendment to the claims.

3. Rejection of claim 7 under 35 U.S.C. 112, 2nd for being indefinite for reciting "Globo-H, fucosyl GM1, KH-1, glycophorin, STn, (2,3)ST, Le^y, Le^x, N3, Tn, 2,6-Stn, Gb3 and TF", is hereby withdrawn in view of Applicant's arguments.

4. Rejection of claims 17-19 under 35 U.S.C. 112m 2nd for being indefinite is hereby withdrawn in view of Applicant's arguments.

Maintained Objection

5. The specification is objected to for the following: The specification indicates "incorporation by reference" of certain documents. The MPEP states the following: "An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference. An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent, >or< (2) a U.S. patent application publication, **>which patent or patent application publication does not itself incorporate such essential material by reference..."Essential material" is defined in >37CFR1.57(c)< as that which is necessary to (1) **>provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C. 112, (2) describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by the second paragraph of 35 U.S.C. 112..." (see MPEP 608.01(p)).

Response to Applicant's Arguments

6. Applicant indicates that "Applicant is unsure of exactly what the Examiner is objecting to, as the Examiner does not elaborate on which documents incorporated by reference would be deemed "essential material"." Applicant requested clarification.

7. Throughout the instant specification, references are "incorporated by reference." For example, at paragraph [0079] of instant specification US 2007/0173636 A1, "small molecules" and drugs for human use listed in FDA under 21 CFR 330,.5, 331 through 361, and 440 through 460 are incorporated by reference; At paragraph [0081] of instant specification US 2007/0173636 A1, listing of classes and specific drugs suitable for practicing present invention may be found in "Pharmaceutical Substances: Syntheses, Patents, Applications" by Azel Kleemann and Jurgen Engel, and "Merck Index: An Encyclopedia of Chemicals, Drugs, and Biological", are incorporated by reference. For example, instant claim 3 recites, "The method of claim 1, wherein each occurrence of A1 and A2 is independently a biomolecule, a small molecule, a macromolecules or a diagnostic label." This is an essential material, which has been incorporated by reference.

Maintained and Revised Rejection

35 U.S.C. 112, 2nd

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

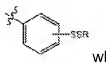
9. Claims 1, 3-4, 7-15, 17, 20-23, 25, 27 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 1 recites, "R^{X0} is a disulfide-substituted aryl moiety". It is unclear what compounds are encompassed within a disulfide-substituted aryl moiety. The instant

specification does not fully define what is meant by a moiety. The dictionary.com defines "moiety" as an indefinite portion, part, or share (see p. 1, enclosed). Therefore, a moiety can be any portion or part of an aryl group, including an alkyl. Therefore, it is unclear what compounds are encompassed within the term "a disulfide-substituted aryl moiety." Claims 3-4, 7-15, 17, 20-23, 25, 27 and 35 depend from indefinite claim 1 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

11. Claim 1 further recites, "...each occurrence of L1 is independently a substituted or unsubstituted, linear or branched, cyclic or acyclic, saturated or unsaturated aliphatic or heteroaliphatic moiety..." It is unclear what compounds are encompassed within a substituted or unsubstituted, linear or branched, cyclic or acyclic, saturated or unsaturated aliphatic or heteroaliphatic moiety. The instant specification does not fully define what is meant by a moiety. The dictionary.com defines "moiety" as an indefinite portion, part, or share (see p. 1, enclosed). Therefore, a moiety can be any portion or part of an aliphatic group, including a carbon atom. Therefore, it is unclear what compounds are encompassed within the term "a disulfide-substituted aryl moiety." Claims 3-4, 7-15, 17, 20-21-23, 25, 27 and 35 depend from indefinite claim 1 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

12. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 17 recites, "the method of claim 9, wherein R^{X0} has the

structure  wherein R is an aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety. It is unclear what compounds are encompassed within "aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety". The dictionary.com defines "moiety" as an indefinite portion, part, or share (see p. 1, enclosed). Therefore, a moiety can be any portion or part of an aliphatic, heteroaliphatic, aromatic or heteroaromatic group.. Therefore, it is unclear what compounds are encompassed within the term "aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety".

Response to Applicant's Arguments

13. Applicant argues that "Applicant has amended claim 1 to recite R^{X0} as being a disulfide-substituted aryl moiety".

14. Applicant's arguments have been fully considered but have not been found persuasive. In regards to "disulfide-substituted aryl moiety", it is unclear what compounds are encompassed within a disulfide-substituted aryl moiety. The instant specification does not fully define what is encompassed within the term moiety, and the definition of moiety from www.dictionary.com indicates that it is a portion or a part of something. Therefore, this can be any part or portion of an aryl molecule.

35 U.S.C. 112, 1st

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1, 3, 8-15, 17-23, 25 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a method for preparing a peptide comprising a peptidic backbone made up of four or more amino acids...each

occurrence of A_1 and A_2 is independently an aliphatic, heteroaliphatic, aromatic, heteroaromatic, aryl, heteroaryl group, R^{X0} is a disulfide-substituted aryl moiety…each occurrence of L1 is independently a substituted or unsubstituted, linear or branched, cyclic or acylic, saturated or unsaturated aliphatic or heteroaliphatic moiety. The generic statements aliphatic, heteroaliphatic, aromatic, heteroaromatic, aryl, heteroaryl group, R^{X0} is a disulfide-substituted aryl moiety…each occurrence of L1 is independently a substituted or unsubstituted, linear or branched, cyclic or acylic, saturated or unsaturated aliphatic or heteroaliphatic moiety do not provide ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claims 1, 3, 8-9, 17 and 21-23 are broad generics with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of compounds, any aliphatic, heteroaliphatic, aromatic, heteroaromatic, aryl, heteroaryl, any class of peptide or a peptide-like molecule that can react with the acyl donor and amide acceptor. Furthermore, the possible structural variations are limitless to any class of compounds that are moieties of aryl, substituted or unsubstituted, linear or branched, cyclic or acylic, saturated or unsaturated aliphatic, heteroaliphatic moieties. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation

between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule or other peptidic molecules that can be peptide linked having pharmaceutical function, and other synthetic peptide or peptide-like molecule, peptidomimetics, amino acid mimetics and other small and macromolecules having pharmaceutical activity.

The specification discloses that "the term aliphatic includes both saturated and unsaturated, straight chain or branched aliphatic hydrocarbons, which are optionally substituted with one or more functional groups (see instant paragraph [0051]). Preferred embodiments are listed in instant paragraph [0052]. The specification discloses that "heteroaliphatic refers to aliphatic moieties in which one or more carbon atoms in the main chain have been substituted with a heteroatom (see instant paragraph [0055]). Instant paragraph [0058] discloses that "the term aromatic moiety refers to stable substituted or unsubstituted unsaturated mono- or polycyclic hydrocarbon moieties having preferably 3-14 carbon atoms (see instant paragraph [0058]); Heteroaromatic

moiety refers to stable substituted or unsubstituted unsaturated mono-heterocylic or polyhetereocyclic moieties having preferably 3-14 carbon atoms (see instant paragraph [0059]). Further, the specification discloses that "aromatic and heteroaromatic moieties, as defined herein, may be attached via an aliphatic (e.g., alkyl) or heteroaliphatic (e.g., heteroalkyl) moiety and thus also include moieties such as (aliphatic) aromatic, -(heteroaliphatic) aromatic, -(aliphatic)heteroaromatic…-(heteroalkyl)heteroaromatic moieties (see paragraph [0060]). The instant paragraph [0062] discloses that "the term heteroaryl refers to heteroaromatic moieties excluding those attached via an aliphatic or heteroaliphatic moiety. The specification discloses that the peptides of the invention are useful in the treatment of disorders, such as anemia (see abstract and paragraphs [0003] and [0049]).

The working examples describe glycan conjugated peptides being chemically ligated together (see Schemes 1-2 and 5-11). The specification does not describe any other A1, and A2 that are aliphatic, heteroaliphatic, aromatic, heteroaromatic, aryl, heteroaryl group, such as synthetic polymers comprising repeating polypeptide units or any other proteins, a polymer of PEG that increases the serum half-life, or any other type of peptide or peptide-like molecule or compounds that act are aliphatic, heteroaliphatic, aromatic, heteroaromatic, aryl heteroaryl or any moieties of aryl, aliphatic or heteroaliphatic, aromatic compounds. Description of glycans, oligosaccharides is not sufficient to encompass numerous other pharmaceutically useful group that belongs to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. In

case of peptide or protein, the number of possible sequences a peptide or protein compounds having a pharmaceutical activity is vast. For example, for a GLP-2 peptide having a 33 amino acid residues, there are $33^{20} = 2.35 \times 10^{30}$ different possibilities including variances and derivatives that have pharmaceutical activity. There are also varying sizes and varying compositions that make up the genus of aliphatic, heteroaliphatic, aromatic, heteroaromatic, aryl, and heteroaryl groups and moieties of such compounds. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to Applicant's Arguments

17. Applicant argues that "restricting the claims to certain A, A1 or A2 groups would represent an undue restriction of the scope of the claims." Applicant argues that "claim scope is not limited to those embodiments actually disclosed in the specification…A

specification may, within the meaning of 35 U.S.C. 112, first paragraph, contain a written description of a broadly claimed invention without describing all species that claim encompasses, and the embodiment need not necessarily have been reduced to practice." Applicant argues that "instant claims are drawn to methods of preparing peptides. Because the claimed invention is not particular peptide compositions or sequences having a particular function, Applicant is unsure of how the Examiner's argument is relevant in the instant case."

18. Applicant's arguments have been fully considered but have not been found persuasive. As Applicant has pointed out, the instant claims are drawn to a method of preparing peptides. The amended claims recite, "disulfide-substituted aryl moiety" and "L1 is independently a substituted or unsubstituted, linear or branched, cyclic or acylic, saturated or unsaturated aliphatic or heteroaliphatic moiety". Again, these can be any compounds that are portions or part of a molecule. The specification does not describe any other A1, and A2 that are aliphatic, heteroaliphatic, aromatic, heteroaromatic, aryl, heteroaryl group, such as synthetic polymers comprising repeating polypeptide units or any other proteins, a polymer of PEG that increases the serum half-life, or any other type of peptide or peptide-like molecule or compounds that act are aliphatic, heteroaliphatic, aromatic, heteroaromatic, aryl heteroaryl or any moieties of aryl, aliphatic or heteroaliphatic, aromatic compounds. Description of glycans, oligosaccharides is not sufficient to encompass numerous other pharmaceutically useful group that belongs to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. In

case of peptide or protein, the number of possible sequences a peptide or protein compounds having a pharmaceutical activity is vast. For example, for a GLP-2 peptide having a 33 amino acid residues, there are $33^{20} = 2.35 \times 10^{30}$ different possibilities including variances and derivatives that have pharmaceutical activity. There are also varying sizes and varying compositions that make up the genus of aliphatic, heteroaliphatic, aromatic, heteroaromatic, aryl, and heteroaryl groups and moieties of such compounds. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed. Since the invention is useful for treatment of such disorders as anemia, the method of instant claims need to produce pharmaceutically active peptides. Since a moiety of an aryl, aliphatic, heteroaliphatic, and aromatic compounds can be anything, there is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

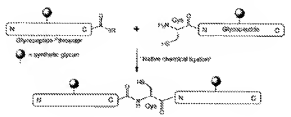
Maintained and Revised

35 U.S.C. 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 1, 3-4, 8-9 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Bertozzi et al (Science, 23 March 2001, 291: 2357-2364, filed with IDS).

21. Bertozzi et al teach glycoprotein synthesis by convergent coupling of glycopeptides fragments,  . Assembly from synthetic glycopeptides fragments using the technique of native chemical ligation. Bertozzi teaches that one fragment is functionalized as a COOH-terminal thioester, and the other bears an NH_2-terminal cysteine residue. A transthioesterification reaction between the two components produces an intermediate thioester that rearranges to the peptide bond shown in the product (see Figure 3(B), p. 2359). Since glycans are pharmaceutically useful group (as disclosed in the specification, see paragraph [07078]), this meets the limitation of claims 1, 3-4, 8-9 and 21.

Response to Applicant's Arguments

22. Applicant argues that "Bertozzi reference teaches "glycoprotein synthesis by convergent coupling of glycopeptide fragment and that one fragment is functionalized as a COOH-terminal thioester." Applicant argues that "the instantly claimed method utilizes a peptide acyl donor comprising a COOH-terminal ester, and not a thioester."

23. Applicant's arguments have been fully considered but have not been found persuasive. The instant claims recite that the R^{X0} is a disulfide-substituted aryl moiety. By applying the broadest reasonable interpretation of the claims, the COOH-terminal thioester can be interpreted as a disulfide substituted aryl moiety. Thus, this meets the

limitation of claims 1, 3-4, 8-9 and 21. Since the in situ intermediate formed would inherently have the Oxygen-substituted aryl moiety when reacted with an amine acceptor, this reference anticipates claims 1, 3-4, 8-9 and 21.

Maintained and Revised

35 U.S.C. 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

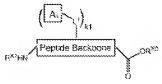
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

26. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

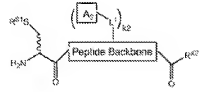
not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

27. Claims 1, 3-4, 8-15, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hojo et al (Tetrahedron Letters, 2003, 44: 2961-2964, filed with IDS) in view of Miller et al (Angewandte, Jan. 27, 2003, 42(4): 431-434, filed with IDS).

28. Hojo et al teach the preparation of peptide thioester carrying N-linked core pentasaccharide by the Fmoc solid phase method with a combination of the benzyl-protection strategy at the carbohydrate portion (see abstract). Hojo teaches the structure of extracellular Ig domain of emmprin carrying pentasaccharide unit 1 (see Figure 1, p. 2961). Hojo teaches that if the glycosylated peptide thioester can be prepared, these methods can be directly applied to the glycoprotein synthesis (see p. 2961, right column). Figure 2 teaches the synthetic procedure of the N-terminal peptide thioester carrying pentasaccharide unit 4 (see p. 2962, right column). Synthetic procedure of the Ig domain (34-94) chemically ligated is taught in Figure 4 (see p. 2963). According to Figure 1, there is at least one cysteine residue between the A-L^1 moieties. Hojo teaches that the N-linked glycopeptides is at the N-terminal end of the Ig domain (34-58) (see Figure 4). The difference between the reference and the instant claims is that the reference does not teach reacting a peptide acyl donor comprising a peptidic backbone made of two or more amino acids wherein said peptide acyl donor



has the structure and with a peptide amino acceptor having the



structure .

29. However, Miller et al teach synthetic N-linked glycoprotein synthesis. Miller teaches building a complex glycodomain and incorporating it into a polypeptide setting, and how the pieces of the puzzle can be interfaced (see p. 432, left column, 1st paragraph). Miller teaches natural O- and N-linkages as opposed to non-natural arrangements…and there is no limit to the structural complexity of the carbohydrate sectors of the glycopeptide targets (see p. 432, left column, 2nd paragraph). Scheme 1 teaches the convergent approach to N-linked glycopeptides using Fmoc synthesis. Scheme 2 teaches the glycan preparation and peptide conjugation. The peptide is Fmoc protected at the N-terminal end and the glycan is conjugated onto the Asn residue of the peptide (see Scheme 2). Scheme 4 teaches the chemical ligation of an N-linked glycopeptides with peptide (see Scheme 4 and p. 433, left column, 2nd full paragraph). Miller teaches in Scheme 4 that ligation was in the presence of PBS and excess sulfanylethane-2-sulfonate (sodium 2-mercaptoethanesulfonate), which is same as the 2-mercaptoethanesulfonic acid. Scheme 5 teaches native chemical ligation of a pentasaccharide glycopeptides and a pentadecapeptide (see Scheme 5 and p. 433, right column, 1st paragraph). Schemes 1-2, 4 and 5 teach that StBu protects the

functional group of the cysteine residue. Miller teaches that the N-linked glycopeptide is at the C-terminal end of the pentadecapeptide (see Schemes 4 and 5).

30. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Hojo et al and Miller et al to produce a polyfunctionalize peptide having multiple N- or O-glycosylated peptides. One of ordinary skill in the art would have been motivated to combine the teachings, since Hojo teaches the method of making a pentasaccharide glycosylated peptide sequence by chemical ligation of two peptide sequences (one that is N-linked glycosylated, and one that is not), and Miller teaches pentasaccharide glycosylated peptide sequence by chemical ligation of two peptide sequences (one that is N-linked glycosylated, and one that is not). Both references teach the importance of glycosylation in a wide range of biological processes. There is a reasonable expectation of success, both teach the pentasaccharide glycopeptide that is glycosylated at the Asn residue. Hojo teaches chemical ligation of an Asn-glycosylated peptide sequence to the N-terminal end of non-glycosylated peptide sequence. Miller on the other hand teaches chemical ligation of an Asn-glycosylated peptide sequence to the C-terminal end of non-glycosylated peptide sequence. One of ordinary skill in the art would expect that both peptide sequences can be glycosylated and chemically ligated, since both N- and C-terminal peptide sequences having glycosylation can be chemically ligated independently.

Response to Applicant's Arguments

31. Applicant argues that "Hojo et al describe the preparation a conjugation of a peptide thioester containing an N-linked core pentasaccharide. Miller et al describes the preparation and conjugation of peptide thioesters. Neither Hojo et al nor Miller et al disclose or teach the activated esters of the present invention." Applicant further argues that "one of ordinary skill in the art would not have been motivated to modify the teachings of Hojo et al and Miller et al to arrive at the presently claimed method which uses activated esters, wherein R^{X0} is a disulfide-substituted aryl moiety."

32. Applicant's arguments have been fully considered but have not been found persuasive. Both Hojo et al and Miller et al teach the active method steps of the instant claims. As indicated above, it is unclear what compounds are encompassed within a disulfide-substituted aryl moiety. By applying the broadest reasonable interpretation of the claims, the COOH-terminal thioester can be interpreted as a disulfide substituted aryl moiety. Thus, this meets the limitation of claims 1, 3-4, 8-15, and 20-22. The in situ intermediate formed would necessarily have the Oxygen-substituted aryl moiety when reacted with an amine acceptor. One of ordinary skill in the art would have been motivated to combine the teachings, since Hojo teaches the method of making a pentasaccharide glycosylated peptide sequence by chemical ligation of two peptide sequences (one that is N-linked glycosylated, and one that is not), and Miller teaches pentasaccharide glycosylated peptide sequence by chemical ligation of two peptide sequences (one that is N-linked glycosylated, and one that is not). Both references teach the importance of glycosylation in a wide range of biological processes. There is a

reasonable expectation of success, both teach the pentasaccharide glycopeptide that is glycosylated at the Asn residue. Hojo teaches chemical ligation of an Asn-glycosylated peptide sequence to the N-terminal end of non-glycosylated peptide sequence. Miller on the other hand teaches chemical ligation of an Asn-glycosylated peptide sequence to the C-terminal end of non-glycosylated peptide sequence. One of ordinary skill in the art would expect that both peptide sequences can be glycosylated and chemically ligated, since both N- and C-terminal peptide sequences having glycosylation can be chemically ligated independently. Therefore, the combined prior arts are prima facie obvious over the instant claims 1, 3-4, 8-15 and 20-22.

Conclusion

33. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Julie Ha/
Examiner, Art Unit 1654